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(54) **Use of histamine derivatives for the preparation of drugs, new histamine derivatives and drugs.**

(57) The use for the preparation of drugs having H_3 histamine receptor agonist properties on the central nervous system of the 4-(4(5)-imidazolyl) butyramidine (compound A), the O-[2-(4(5)-imidazolyl)-ethyl] isourea (compound C) the S-[2-(4(5)-imidazolyl) ethyl] isothiourea (compound E)as well as their N-methyl derivatives (compound B, D, F), and new compounds B, C, D, being useful for the preparation of drugs to be used as anti-migraine hypnotic, sleep-inducer, tranquillizer, sedative, anxiolytic, anti-asthmatic and anti-inflammatory agents, notably for the bronchi, the skin or the eyes, or as anti-gastric ulcer agents, and drugs comprising these compounds.

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This invention relates to the therapeutic use of histamine derivatives, new histamine derivatives and the use of these derivatives for the preparation of drugs.

In 1983 Arrang et al. (Nature, 1983, 302, 832) detected the xistence of a third histamine receptor called H_3.

European patent application EP-A-0 420 396, teaches that S-[2-(4(5)-imidazolyl) ethyl] isothiourea and 4-(4(5)-imidazolyl) butyramidine are highly potent selective histamine H_3-agonists and provides use of these compounds for treating allergic disease and gastrointestinal motility disorders.

Although it was believed, as a theoretical knowledge, that agonists of the H_3-receptor of histamine may inhibit the synthesis and release of neurotransmitters such as histamine in the central nervous system, no individual H_3-agonist was ever used for such central indication.

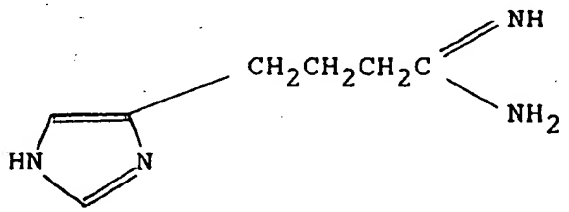
Further it was not apparent that these known compounds may cross the blood-brain barrier and be active in the brain. Also compounds having chemical structures close to these compounds were known to be unable to cross the blood-brain barrier.

Only in EP-A-0 458 661, published after the convention priority date of the present application, it was for the first time disclosed that S-[2-(4(5)-imidazolyl) ethyl] isothiourea and its N-methyl derivative could adequately cross the blood-brain barrier and, further, was a suitable component for preparing an efficient drug to be used as a tranquillizer, sleep-inducer, hypnotic, sedative, and anxiolytic, agent.

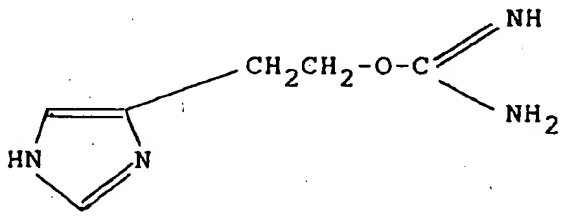
Treatment of migraine by the usual drugs is often of poor efficiency and is still difficult.

Object of the invention is the use of at last one of the following compounds for the preparation of a drug to be used as an anti-migraine tranquillizer, sleep-inducer, hypnotic, sedative, anxiolytic, anti-asthmatic and anti-inflamatory agent, notably for the bronchi, the skin or the eyes, or as an anti-gastric ulcer agent:

- Compound A : 4-(4(5)-imidazolyl butyramidine



- Compound B : the N-methyl derivative of compound A
- Compound C : 0-[2-(4(5)-imidazolyl)ethyl] isourea

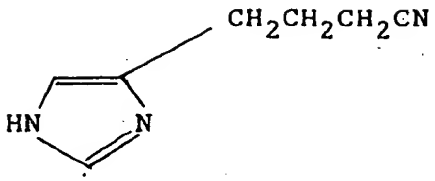


- Compounds D : the N-methyl derivative of compound C
- Compounds E : the S-[2-(4(5)-Imidazolyl) ethyl] Isothiouera
- Compound F : the N-methyl derivative of compound E, provided that when compounds E or F are used alone they are used for the preparation of a drug to be used as an agent against migraine.

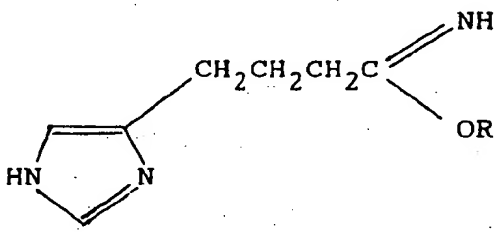
Although the prepared agent has gastric (including duodenal) anti-ulcer properties also associated to the action as a peripheral H_3 agonist, its efficiency is largely related to the sedative effects on the central nervous systeme.

Another object of the invention is to provid new chemical compounds which are useful to prepare drugs able to cross the blood-brain barrier and to act as histamine agonists on the H_3 rec pt r.

The new compounds according to the inv ntion are select d from the group consisting of compounds B, C and D. The compound B, which is N-methyl-4[4(5)-imidazolyl] butyramidine, may be prepared from the nitrile of formula



Treatment of the nitrile under anhydrous conditions in the presence of a strong acid (which may be introduced in gaseous form into the reaction mixture) with an alcohol ROH e.g. methanol or ethanol gives an iminoether of following formula,



wherein R is, for example, methyl or ethyl, which may be treated with methylamine to yield the required amidine.

Alternatively, treatment of the nitrile at elevated temperature with a methylammonium salt gives the required amidine compound directly.

Example 1 is a particularly preferred embodiment of the method.

Example 1

N-Methyl-4(4(5)-imidazolyl)butyramidine ditrifluoroacetate hydrate.

To a solution of 3-(4(5)-imidazolyl)propionitrile (0.5 g) in absolute ethanol (15 ml) was added dry hydrogen chloride at 0-5°C for 2 hours and the mixture was allowed to stand for 18 hours in a refrigerator. The solvent was evaporated under reduced pressure and the residual solid was crystallised from ethanol-diethyl ether to aford ethyl 3-(4(5)-imidazolyl)propionimidate dihydrocloride (0.94 g).

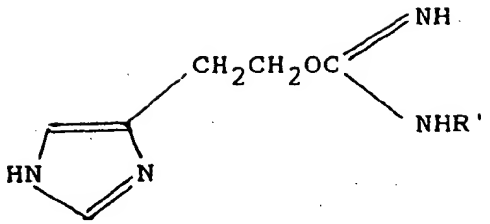
A solution of ethyl 3-(4(5)-imidazolyl) propionimidate dihydrochloride (130 mg, 0.5 mmol) in freshly distilled ethanol (5 ml) was chilled to -5°C in an ice salt bath and treated with 1 ml of ethanolic methylamine solution (methylamine was bubbled for 0.5 minute into ethanol at 0°C). The solution was stirred at 0°C for 2 hours and refrigerated overnight. The solvent was evaporated under reduced pressure to afford a solid residue which was chromatographed under high pressure using water containing 1 % methanol and 0.1 % trifluoroacetic acid on a Kromasil C_{18} column to yield the required product as an oil which was dried in vacuo for 16 hours at 40°C.

^{1}H NMR: (D_2O, 400 MHz); δ (ppm) 8.50 (s, 1H, Im-2H); 7.20 (s, 1H, Im-4(5)H); 2.90 (s, 3H, CH_3); 2.80 (t, 2H, CH_2Amidine); 2.54 (t, 2H, Im-CH_2); 2.05 (quint, 2H, CH_2).

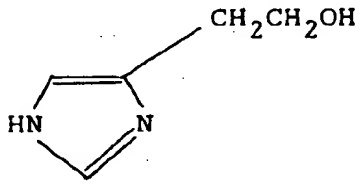
Mass spectrum : (FAB); m/e 167$(M+H)^+$

Analysis:			
Calc: for $C_8H_{14}N_4$, $2CF_3CO_2H$, H_2O,	C 34.96	H 4.40	N 13.59
Found:	C 35.04	H 4.49	N 13.61

Compound C or D of formula



wherein R' = H or methyl may be prepared by treating cyanamide (H_2NCN) or methyl cyanamide (CH_3-HNCN) with a hydrohalide salt of the compound 2-[4(5)-imidazolyl] ethan-1-ol (formula hereunder) under anhydrous acidic conditions.



Examples 2 and 3 are particulary preferred embodiments of the method.

Example 2

O-[2-(4(5)-(Imidazolyl)ethyl] isourea dihydrochloride

4(5)-(2-hydroxyethyl)imidazole (0.5 g, 4.46 mmol) and cyanamide (0.375 g, 8.92 mmol) were stirred in benzene (which had been dried over a molecular sieve) (50 ml) saturated with dry hydrogen chloride (until the fumes turned universal indicator paper red) at 20°C. After 4 days, the mixture reaction was heated at 50°C. Two days later, chloroform (20 ml) was added, stirring and heating at 50°C continued for 1 day. Then more hydrogen chloride was added and the mixture heated at 50°C for a further 7 days. The reaction mixture was then cooled and the solvent decanted. The residue was recrystallised from ethanol: diethyl ever mixture and then recrystallised from ethanol to give the compound named above, m.p. 164-166°C.

^{1}H NMR: (DMSO-d_6, 400 MHz); δ (ppm) 9.06 (s, 1H, Im-2H); 8.72 (s, 4H, Im-NH and isourea-NH,NH_2); 7.53 (s, 1H, Im-4(5)H); 4.53 (t, 2H, CH_2-O): 3.10 (t, 3H, Im-CH).

Mass spectrum: (FAB); m/e 155 $(M+H)^+$

Analysis:	Calc: for $C_6H_{10}N_4O$, 2HCl, 0.1C_2H_5OH			
	C 32.14;	H 5.48;	N 24.18;	Cl 30.60
Found :	C 32.24;	H 5.24;	N 24.33;	Cl 30.63

Example 3

N-Methyl-O-[2-(4(5)-(Imidazolyl)ethyl] isourea ditrifluoroacetate monohydrate

A solution of cyanogen bromide (5.30 g, 50 mmol) in diethyl eher (dried over sodium) (40 ml) cooled at -3-10°C was placed in a three-necked flask fitted with magnetic stirrer and thermometer; dry methylamine gas was bubbled in slowly with stirring and under nitrogen. The bubbling was continued for two hours, keeping the reaction temperature at -3-10°C by cooling. At the end of the reaction, the flow of methylamine gas was cut off entirely when the pH of the mixture reached about 7. The resulting mixture was filtered and the ether removed under reduced pressure at low temperatur (below 5°C because the compound is volatile) in the dark to leave a liquid which was dissolved in ether (5 ml), filtered and evaporated. The residue was recrystallized from ether in a vessel containing a solid carbon dioxide cold finger to give N-methyl cyanamide.

To a suspension of 4(5)-(2-hydroxyethyl)imidazole (0.4 g, 3.6 mmol) in benzene (dried over sodium) (50 ml) saturated with dry hydrogen chloride, was added a solution of an excess of N-methyl cyanamide in benzene (dried over sodium) (20 ml) saturated with dry hydrogen chloride (until the fumes turned universal indicator

paper red) at 20°C. The reaction mixture was stirred at room temperature for 15 days in a sealed flask. The solv nt was decant d and the oily residue was subjected to chrom tography under high pressure on a Kromasil C_{18} column using water containing 0.1 % trifluoroacetic acid for lution to yield the product which was isolated as a syrup and was dried in vacuo at 30° for 70 hours.

^1H NMR: (D_2O, 400 MHz, 75°C); δ (ppm) 8.55 (s, 1H, Im-2H); 7.33 (s, 1H, Im-4(5)H): 4.56 (s, 2H, OCH_3); 3.25 (s, 2H, $ImCH_2$); 2.85 (s, 3H, NCH_3).

Mass spectrum: (FAB); m/e 169 $(M+H)^+$

Analysis: Calc: for $C_7H_{12}N_4O$, $2.5CF_3CO_2H$, H_2O:

C 30.58; H 3.53; N 11.89;

Found : C 30.85; H 3.26; N 12.29

Another object of the invention is a drug comprising an efficient amount of compounds B, C or D which is an hypnotic, sleep-inducer, tranquillizer, sedative or anxiolytic drug or an anti-asthmatic or an anti-inflammatory notably for the bronchi, the skin or the eyes, or an anti-gastric ulcer drug.

These drugs are notably active at a dose between about 0.1 and 30 mg/kg.

A preferred dosage unit for an anti-migraine hypnotic, sleep-inducer, tranquillizer, sedative or anxiolytic drug comprises, in an usual suitable form, from 5 or 6 mg to 500 or 600 mg of compounds A, B, C, D, E or F, where a dosage from 5 or 6 mg to 50 or 60 mg is more preferred for compounds A or C and a dosage of 0.3 to 3 mg/kg, preferably 1 mg/kg is preferred for compounds E and F for oral route administration, and 0.15 to 1.25 mg/kg, preferably 0.5 mg/kg for parenteral route administration, and 5 to 50 mg for intranasal route administration.

The drugs prepared according to the invention may be administered to man in association with a pharmaceutically acceptable excipient or vehicule, as an anti-migraine tranquillizer, sleep-inducer, hypnotic, sedative, anxiolytic anti-asthmatic and anti-inflamatory agent, notably for the bronchi, the skin or the eyes, or as an anti-gastric ulcer agent.

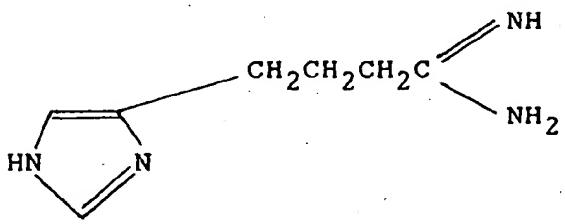
For the preparation of the inventive drugs the compound, once dosed, is mixed with excipients and vehicles as commonly used for the intended oral, parenteral or topical administration.

Of course the above definitions of the compounds encompass obvious equivalents such as their pharmaceutically acceptable salts.

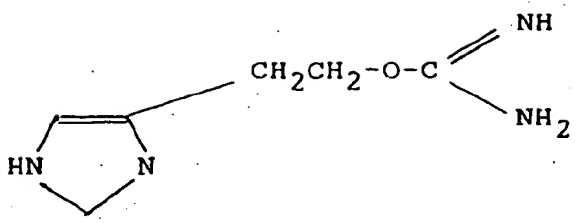
Claims

1. The use of at least one of the following compounds for the preparation of a drug to be used as an anti-migraine tranquillizer, sleep-inducer, hypnotic, sedative, anxiolytic, anti-asthmatic and anti-inflamatory agent, notably for the bronchi, the skin or the eyes, or as an anti-gastric ulcer agent:

- Compound A : 4-(4(5)-imidazolyl butyramidine



- Compound B : the N-methyl derivative of compound A
- Compound C : 0-[2-(4(5)-imidazolyl)ethyl] isourea



- Compound D : the N-methyl derivative of compound C
- Compound E : the S-[2-(4(5)-imidazolyl) ethyl] isothiourea
- Compound F : the N-methyl derivative of compound E, provided that when compounds E or F are used alone they are used for the preparation of a drug to be used as an agent against migraine.

2. The new compounds selected from the group consisting of compounds B, C and D as defined in claim 1.

3. A drug which is active as an hypnotic, sleep-inducer, tranquillizer, sedative, anxiolytic, anti-asthmatic, anti-inflammatory, notably for the bronchi, the skin or the eyes, or as an anti-gastric ulcer agent comprising an efficient amount of the N-methyl derivative of 4-(4(5)-imidazolyl) butyramidine (B) or the O-[2-(4(5)-imidazolyl)-ethyl] isourea (C) or its N-methyl derivative (D).

4. A drug according to claim 3 comprising said compound at a dose between 0.1 and 30 mg/kg.

5. A drug according to claim 4 comprising said compound at a dose between 5 or 6 mg and 500 or 600 mg.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 40 2418

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,P, X D,P, Y	EP-A-0 458 661 (SOCIETE CIVILE BIOPROJET) * claims 3-5 *	1 2-3	A61K31/415 C07D233/64
D,X D,Y	EP-A-0 420 396 (SMITH KLINE & FRENCH LABORATORIES LTD.) * page 4, line 30 - line 44; claims 6-8 *	1 1-3	
X	US-A-3 891 764 (SMITH KLINE & FRENCH LABORATORIES LTD.) * column 3, line 15 - line 20; example 6 *	1	
Y	US-A-3 759 944 (SMITH KLINE & FRENCH LABORATORIES LTD.) * column 2, line 48 - line 62; claim 1; example 4 *	1-2	
Y	US-A-4 000 302 (SMITH KLINE & FRENCH LABORATORIES LTD.) *table 3, example 7*	2	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
Y	GB-A-1 296 544 (SMITH KLINE & FRENCH LABORATORIES LTD.) * claims 1-5; example 4 *	2	A61K C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	11 NOVEMBER 1992	FOERSTER W.K.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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